REMARKS

Claims 1-40 were presented in the original application. In Applicant's election and reply to the restriction requirement in the Office Action dated April 8, 2008, Applicant provisionally elected the Group 1 claims without traverse. In the Office Action dated September 15, 2008, the Office vacated the previous restriction requirement and provided a substitute restriction requirement. In response to this second Office Action, Applicant provisionally elected the Group I invention with traverse and elected without traverse the species *fur* and 1-Δ(gmd-fcl)-26 for the purpose of examination. In a third Office Action containing only a restriction requirement, the Office again vacated its previous restriction requirement and provided another substitute restriction requirement.

AMENDMENTS TO THE CLAIMS

Claim 23 has been amended to correct a typographical error. The word "is" has been added where it was previously inadvertently omitted. Claims 1, 12, 19, 21, 23, 32, and 33 have been amended by substitution of the phrase "consisting essentially of" with the term "comprising". Support for the substitution of the phrase "consisting essentially of" with the term "comprising" in these claims can at least be found in the specification as filed in the paragraph spanning Page 18-19; at Page 21, l.4-6; in the first complete paragraph of Page 22, and in the first complete paragraph of Page 23. Claims 27-30 are canceled herewith.

PATENT TERM ADJUSTMENTS UNDER 35 USC §154 AND 37 CFR §1.703.

Applicants respectfully submit that the entire delay in prosecution extending from the Applicant's response of February 9, 2008 in good faith to the second Restriction of April 8, 2008 until the USPTO mailing of the third restriction Office Action of June 1, 2009 vacating the second Restriction and imposing a third Restriction constitutes a delay in prosecution by the Office. This period of delay occurred when the Office issued a third Restriction that vacated the Office's second Restriction of April 8, 2008 following Applicant's good faith response.

Applicants therefore respectfully request that this delay extending from February 9, 2009 to June 1, 2009, as well as any previous delays in prosecution by the Office, be properly accounted for in any subsequent calculations of Patent Term pursuant to 35 USC §154 and 37 CFR §1.703 that are applicable.

Applicants also respectfully note for the record that this and all previous Restrictions under 37 CFR § 1.141 do not constitute an action under 35 USC §132 or 35 USC §151. Applicants therefore request that the number of days in the period between April 24, 2008 and until the date of a subsequent and first occurring Office Action under either 35 USC §132 or 35 USC §151 be properly credited toward any extension in Patent Term due to the applicant pursuant to 35 USC §154 (A)(i) and 37 CFR §1.703(a)(1).

ELECTION/RESTRICTIONS

In the Restriction dated June 1, 2009, the Office alleged that the pending claims encompass the following ten groups of inventions that allegedly "do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features":

Group I.	Claims 1 and 8-10.
Group II.	Claims 2-7 and 33.
Group III.	Claim 11.
Group IV.	Claims 12-16, 19, 21-22.
Group V.	Claims 23-25.
Group VI.	Claims 27-32.
Group VII.	Claims 34-37.
Group VIII.	Claims 38-39.
Group IX.	Claim 40.
Group X.	Claim 17.

Applicant hereby provisionally elects *with* traverse the Group I invention. Applicant identifies claims 1 and 8-10 as the claims corresponding to this election. The claims of the Group I invention – **as amended** and previously presented in Applicant's response dated February 9, 2009 – are drawn to "a live attenuated derivative of a pathogenic *Salmonella* species consisting essentially of (a) a means for regulatable expression of a *fur* gene that encodes a regulatory protein, wherein said gene is expressed when said attentuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella* species and *E. coli* strains and (b) a means for regulatable synthesis of a first carbohydrate antigen, wherein said first carbohydrate antigen ceases to be synthesized in vivo, exposing a second carbohydrate antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains."

Applicant notes several discrepancies in the current Office Action and traverses the restriction requirement for the following reasons.

First, the Office's description of Group I, claims 1 and 8-10, and Group II, claims 2-7 and 33, is verbatim the same. According to the language of the Office Action, the Group I invention and Group II invention are drawn word-for-word to the same subject matter. Therefore, Applicant can find no rationale supporting restriction between Group I and Group II. In fact, the Office Action as written formally admits that the alleged Group I and Group II claims are drawn to the same invention. Thus, Applicant respectfully requests that the requirement for restriction between them be withdrawn and that claims 2-7 and 33 be examined with the claims of the elected Group I invention.

Second, Applicant notes that claim 26 has not been designated within one of the ten groups of inventions. Claim 26 is a dependent claim drawn to the same live attenuated derivative of claim 1 and contains all of the limitations of claim 1. Therefore, because claim 26 is drawn to the same invention of claim 1, Applicant requests that claim 26 be examined with the elected Group I invention.

Applicant also respectfully notes that although the current Office Action indicates that it is responsive to Applicant's Amendment and Response filed February 9, 2009 (page 2, heading I. of the current Office Action), the language of the current Office Action does not appear to consistently reflect amendments made to claim 1 in Applicant's previous Amendment and Response. Applicant finds this omission especially notable because, as previously argued in Applicant's response of February 9, 2009, *all* of the claims – independent and dependent – incorporate the feature that the regulatable *fur* gene is expressed when the attenuated strain is in the intestinal tract of an individual and the gene is not expressed when the attenuated strain is within internal tissues. This feature is thus a "special technical feature" that provides a common technical relationship among all of the currently pending claims for purposes of unity of invention. (PCT Rule 13.2)

In addition to the preceding oversight, the Office Action states that the technical feature of linking the various groups is "the mutation of various genes within a Salmonella species in order to get regulatable expression." (page 6, heading III.11. of the current Office Action). Because the Office Action fails to also acknowledge that the feature of – the *fur* gene being expressed when the attenuated strain is in the intestinal tract of an individual and the gene not being expressed when the attenuated strain is within internal tissues – is also a special technical feature common to all the claims, the Applicant respectfully contends that the Office has misrepresented the technical features of the claims. The aforementioned feature defines a contribution which each of the claims – when considered as a whole – makes over the prior art.

Further, the Office Action fails to address Applicant's previously reasoned explanation of why such feature is a special technical feature linking the currently pending claims to form a single inventive concept under PCT Rule 13.2 (page 11, paragraphs 1 and 2 of Applicant's Amendment and Response filed February 9, 2009). It appears that the current Office Action fails to fully consider Applicant's previously filed amendments and response. Therefore, Applicant respectfully asserts that the current requirement for restriction lacks basis and Applicant requests that the entirety of the current restriction requirement be withdrawn. All of the currently pending claims share the aforementioned special technical feature and form a single general inventive

concept. Applicant thus requests that all of the currently pending claims – i.e., claims 1-6, 8-12, 14-17, 19, and 21-40 be examined on the merits together in the current application.

In the present Action, the Office alleges that the instant invention does not make a contribution over the art of Simpson et al (U.S. Patent No. 6,521,441), Curtiss et al (WO 1991/006317), and Curtiss et al (WO 2001/83785A2), and hence there is no unity of invention (pages 6-8, paragraph 12 of the current Office Action). The Office alleges that it "would have been *prima facie* obvious to one of skill in the art to insert the fur gene as taught by Simpson et al into the vector and operably linked to a regulatable promoter as taught by Curtiss et al...." Applicant respectfully notes that all of the pending claims – both independent and dependent – as amended now incorporate the feature that the regulatable *fur* gene is expressed when the attenuated strain is in the intestinal tract of an individual and the gene is not expressed when the attenuated strain is within internal tissue. As admitted by the Office in the current Office Action, neither Simpson et al or either of Curtiss et al (1991) or Curtiss et al (2001) teach or suggest this feature.

The Office alleges that it would have been obvious to one of skill in the art to combine Simpson et al with Curtiss et al (2001). Such a combination is not obvious for a number of reasons. First, there is a high degree of unpredictability in the field of developing recombinant attenuated bacteria with the ability to elicit immune responses. For instance, the field has struggled with the fact that mutation of virulence genes often decreases the effectiveness of bacteria when used as live vaccines (pages 2-3 of the specification). Therefore, the Office's allegation of a *prima facie* case of obviousness is not supported because Applicant's invention is not a combination of prior art elements according to known methods to *yield predictable results*, nor is it a simple substitution of one known element for another to obtain *predictable results*. (MPEP § 2143 *Examples of Basic Requirement of a Prima Facie Case of Obviousness*; see also *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727 (2007)). Further, the this case does not fall into the category of being obvious as a result of being "obvious to try" according to the Federal Circuit in the recent case of *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

> [T]his court outlined two classes of situations where "obvious to try" is *erroneously equated with obviousness* under § 103. In the first class of cases, what would have been "obvious to try" would have been to vary all parameters *or try each of numerous possible choices* until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or *no direction as to which of many possible choices is likely to be successful.*

Id. (emphasis added) As admitted by the Office, Simpson et al merely discloses *Staphlococcus aureus fur* genes and fails to disclose any of the other features of the invention as claimed. Curtiss et al 2001 describes a very distinct use of the araCPBAD promoter to drive expression of a repressor protein that controls replication of an *exogenously* provided recombinant DNA vector. In contrast, the araCPBAD promoter is used in the instant application to drive the expression of the fur or other regulatory genes that control various *endogenous* bacterial genes. The instant invention does not entail use of fur to regulate an *exogenously* provided recombinant DNA vector. Moreover, the applicants have found that the combination of an araCPBAD promoter and the fur regulatory gene provides for optimized live vaccine preparation and performance. The prior art does not contain direction as to why the choice of the *fur* gene, out of the multitude of other potential genes disclosed in the literature at the time of filing, was likely to be successful. As cautioned against by the court in *Kubin*, "[one] should not succumb to hindsight claims of obviousness." *Id.*

In addition, Applicant respectfully directs the Office to MPEP § 1850 II. which states:

> Although lack of unity of invention should certainly be raised in clear cases, it should *neither be raised nor maintained on the basis of a narrow, literal or academic approach.* There should be broad, practical consideration of the degree of interdependence of the alternatives presented, in relation to the state of the art.... If the common matter of the independent claims is well known and the

> remaining subject matter of each claim differs from that of the others without there being any unifying novel inventive concept common to all, then clearly there is lack of unity of invention. If, on the other hand, there is a single general inventive concept that appears novel and involves inventive step, then there is unity of invention and an objection of lack of unity does not arise. For determining the action to be taken by the examiner between these two extremes, rigid rules cannot be given and each case should be considered on its merits, *the benefit of any doubt being given to the applicant.* (emphasis added).

As explained above and in Applicant's previous Amendment and Response, Applicant has provided a novel and inventive special technical feature providing a shared technical relationship among all of the claims. The Office has failed to rebut this technical relationship. Further, it cannot be said that the issues that are raised by the Office present a clear or undisputable case. According to the MPEP, Applicant is entitled to the benefit of the doubt. Applicant also respectfully reminds the Office that the standard for determining unity of invention under PCT Rule 13 is not the same as an obviousness rejection under 35 U.S.C. § 103. Therefore, Applicant respectfully requests that the Office withdraw the current requirement for restriction and examine the invention consisting of all the pending claims – all of which share a special technical feature – in the current application.

The Office has also designated several groups of inventions consisting of dependent claims (e.g., Groups VI, VII, VIII, and IX). PCT Rule 13.4. Dependent Claims states:

> Subject to Rule 13.1, it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention claimed in an independent claims, *even where the features of any dependent claim could be considered as constituting in themselves an invention.* (emphasis added)

Therefore, Applicant respectfully asserts that the Office's restriction of dependent claims is inappropriate and contrary to the clear language of PCT Rule 13.4. Applicant requests that restriction of the dependent claims be withdrawn and that these dependent claims be examined on the merits with the entirety of the currently pending claims.

In addition, Groups III and X (claims 11 and 17 respectively) are method claims that use the live attenuated derivative claimed in claim 1 and therefore incorporate by reference to claim 1 all of the limitations including the special technical feature of claim 1. MPEP § 1850 I. *The Requirement for "Unity of Invention"* states:

> In applying PCT Rule 13.2 to international applications as an International Searching Authority, an International Preliminary Examining Authority and to national stage applications under 35 U.S.C. 371, examiners should consider for unity of invention all the claims to different categories of invention in the application and permit retention in the same application for searching and/or preliminary examination, claims to the categories which meet the requirements of PCT Rule 13.2.

Further, MPEP § 1850 III.A. *Combinations of Different Categories of Claims* explains:

> The method for determining unity of invention under PCT Rule 13 shall be construed as permitting in particular, the *inclusion* of any one of the following combinations of claims of different categories in the same international application:
>
> (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and *an independent claim for a use of the said product*... (emphasis added)

Again, Applicant respectfully requests that the Office's restriction of claims 11 and 17 for the use of the live attenuated derivative claimed in claim 1 be withdrawn and that the claims be examined on the merits with the entirety of the currently pending claims.

ELECTION OF SPECIES

Applicant hereby elects *with* traverse the following species for the purposes of examination. As specified on page 8, paragraph 13 of the Office action, because Applicant has provisionally elected the Group I invention, Applicant provisionally elects the combination of the *fur* gene that encodes a regulatory protein and LPS O-antigen as the carbohydrate for the purpose of examination. Applicant respectfully disagrees with and traverses the Office's assertion that "examination be restricted to only the elected gene or combination thereof (if applicable) and should not be construed as a species election." (page 8, paragraph 13 of the current Office Action).

First, the Office Action cites MPEP §803.04 which is drawn to restriction of claims directed to specific *nucleotide sequences* in support of the species election requirement. The relevance of this section of the MPEP to claims that are not nucleotide sequence claims is unclear, particularly where the species identified by the Office Action include carbohydrates.

Second, it is noted that many of the claims to which this gene election requirement is directed are Markush claims (i.e. claims 3, 36, 37, and 38) where sections of the law outlined in MPEP § 803.02 are pertinent. More specifically, that section of the MPEP states:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require provisional election of a single species. >See MPEP § 808.02.

> Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility. (MPEP § 803.02)

In this case, the members of the Markush groups of claims 3, 36, 37, and 38 share a common utility. More specifically, the *fliC* and *fljB* mutants of claim 3 are related both structurally and functionally in that they encode mutant flagella as described on page 13 of the specification as filed. Furthermore, search and examination of the two members of claim 3 can be made without serious burden. Applicant nonetheless provisionally elects with traverse *fliC* for the sole purpose of compliance with the Restriction and advancing prosecution. The members of the Markush groups of claims 36 and 37 are genes that provide for biological containment as per Example 19 and Table 11 on pages 61-65 of the specification. Applicant nonetheless provisionally elects with traverse Δ(*gmd-fcl*)-26 (claim 36) and *gmd* (claim 37) for the sole purpose of compliance with the Restriction and advancing prosecution. The members of the Markush group of claim 28 are *sip* and *sop* genes that block the ability of *S. typhimurium* and *S. dublin* to cause fluid secretion resulting in diarrhea as per Example 20 on page 67 of the specification. Search and examination of the two members of claim 28 can be made without serious burden. The members of the Markush group of claim 38 are *sip* and *sop* genes that block the ability of certain *Salmonella* to cause fluid secretion resulting in diarrhea as per Example 20 on page 67 of the specification. Applicants nonetheless provisionally elect with traverse *sop* for the sole purpose of compliance with the Restriction and advancing prosecution. Given the common utilities shared by members of the Markush groups of claims 3, 36, 37, and 38, withdrawal of the species election requirement is respectfully requested.

Furthermore, PCT Rule 13.4 allows for the inclusion of dependent claims, *even where the features of any dependent claim could be considered as constituting in themselves an invention.* Thus, the gene election requirement imposed by the Office is improper under PCT Rule 13.4 as it precludes the consideration of dependent claims to which the Applicant is entitled. Thus, Applicant respectfully requests that the requirement to elect a gene or combination thereof also be withdrawn.

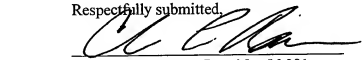
CONCLUSION

Applicant believes that a complete response to the Office Action of June 1, 2009 is provided herewith and respectfully request that the Office withdraw the Restriction of that Office Action in light of the traversals provided herein. Nonetheless, should the Office maintain the Restriction, Applicant further respectfully requests examination on the merits of the provisionally elected claims and provisionally elected Markush group members provided herein to spare the Applicant further delay and expense.

It is not believed that extensions of time are required beyond those which may otherwise be provided for in this filing. In the event however that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. §1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account 20-0823.

The Examiner is encouraged to contact the undersigned via telephone at the number provided, if it is determined that personal communication will expedite prosecution of this application.

Respectfully submitted,



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Dated: August 3, 2009